protein of *A. terreus* (SEQ ID NO:91) are identified by the invention described herein. Mutations at residues 31, 41, 52, 73, 101, 111, 133, 141, 153, 281, 367, and 389 of the wild-type lovE protein of *A. terreus* have been identified as being critical for the improvement of *lovE* regulator protein function. Those mutations include: F31L, Q41K, Q41R, T52I, T52N, C73R, P101S, P101Q, V111I, S133L, E141V, E141K, C153Y, C153R, T281A, N367I, N367Y, P389S and P389L. Each mutation, therefore, represents a change of one conservative class of amino acids for another. For example, the mutation F31L represents a change from a Group 6 amino acid residue to a Group 2 amino acid residue at position 31 of the wild-type, lovE regulator protein.

Thus, by way of non-limiting example, regulator proteins of this aspect of the invention include at least one of the following mutations: (1) a Group 6 amino acid residue mutated to a Group 2 amino acid residue at position 31, for example, the mutation represented by F31L;(2) a Group 3 amino acid residue mutated to a Group 5 amino acid residue at position 41, for example, the mutation represented by Q41K or Q41R; (3) a Group 4 amino acid residue mutated to a Group 2 amino acid residue at position 52, for example, the mutation represented by T52I; (4) a Group 4 amino acid residue mutated to a Group 3 amino acid residue at position 52, for example, the mutation represented by T52N; (5) a Group 4 amino acid residue mutated to a Group 5 amino acid residue at position 73, for example, the mutation represented by C73R; (6) a Group 1 amino acid residue mutated to a Group 4 amino acid residue at position 101, for example, the mutation represented by P101S; (7) a Group 1 amino acid residue mutated to a Group 3 amino acid residue at position 101, for example, the mutation represented by P101Q; (8) a valine amino acid residue mutated to another Group 2 amino acid residue at position 111, for example, the mutation represented by V111I; (9) a Group 4 amino acid residue mutated to a Group 2 amino acid residue at position 133, for example, the mutation represented by S133L; (10) a Group 3 amino acid residue mutated to a

Group 2 amino acid residue at position 141, for example, the mutation represented by E141V; (11) a Group 3 amino acid residue mutated to a Group 5 amino acid residue at position 141, for example, the mutation represented by E141K; (12) a Group 4 amino acid residue mutated to Group 6 amino acid residue at position 153, for example, the mutation represented by C153Y; (13) a Group 4 amino acid residue mutated to a Group 5 amino acid residue at position 153, for example, the mutation represented by C153R; (14) a Group 4 amino acid residue mutated to a Group 1 amino acid residue at position 281, for example, the mutation represented by T281A; (15) a Group 3 amino acid residue mutated to a Group 2 amino acid residue at position 367, for example, the mutation represented by N367I; (16) a Group 3 amino acid residue mutated to a Group 6 amino acid residue at position 367, for example, the mutation represented by N367Y; (17) a Group 1 amino acid residue mutated to Group 4 amino acid residue at position 389, for example, the mutation represented by P389S; and/or (18) a Group 1 amino acid residue mutated to a Group 2 amino acid residue at position 389, for example, the mutation represented by P389L.

In other embodiments of the first aspect, the invention provides a variant of the lovE regulator protein with at least two, or at least three, or at least four, or at least five, or at least six, or at least seven, or at least eight, or at least nine, or at least ten, or at least eleven, or at least twelve, or at least thirteen, or at least fourteen, or at least fifteen, or at least sixteen, or at least seventeen, or at least eighteen of the above described specific mutations.

In other embodiments of the first aspect, the invention provides an isolated lovE variant regulator protein having the sequence of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58,

SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, or SEQ ID NO:65.

In a second aspect, the invention provides a nucleic acid molecule encoding a variant regulator protein of secondary metabolite production of the first aspect of the invention. As used herein, the terms "nucleic acid" or "nucleic acid molecule" refer to a deoxyribonucleotide or ribonucleotide polymer in either single-or double-stranded form, and unless otherwise limited, would encompass analogs of natural nucleotides that can function in a similar manner as the naturally occurring nucleotide.

In one embodiment of the second aspect, the invention provides a nucleic acid molecule encoding a variant protein of the lovE regulator protein of the first aspect of the invention.

By way of non-limiting example, the invention provides a nucleic acid molecule encoding a lovE variant regulator protein having the sequence of SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, or SEQ ID NO:90.

Poor transformation efficiency and the lack of efficient selection systems frequently precludes the screening of large numbers of variant regulator proteins of secondary metabolites in the organism from which the regulator protein is isolated. For example, there are currently certain technical obstacles to the successful screening of large numbers of variant regulator proteins in the fungus *A. terreus*, an organism that produces the secondary metabolite lovastatin.

The invention described herein takes advantage of the genetically tractable and experimentally amenable organism *Saccharomyces cerevisiae* for screening large numbers of variant regulator proteins of secondary metabolite production. Techniques common to the field of molecular biology are well developed in *S. cerevisiae*, and large